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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/683,576	10/10/2003	Stephen F. Vatner	601-1-137	9455

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KLAUBER & JACKSON
411 HACKENSACK AVENUE
HACKENSACK, NJ 07601

EXAMINER	
MONDESI, ROBERT B	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 05/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/683,576	VATNER ET AL.	
	Examiner	Art Unit	
	Robert B. Mondesi	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *18-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 October 2003 and 19 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to restriction requirement

Applicants' election with traverse of Invention Group I, Claims 1-17 in amendment, filed February 14, 2005 is acknowledged. The traversal is on the ground(s) that The search for any of the methods separately classified by the examiner as the invention of Group II would require an additional search of the identical classes wherein method of Group I are classified, thus resulting in a duplicate search of the same material.

This is not found persuasive because the invention of Group I is drawn to a method of *in vivo* treatment of mammals for cardiac disease involving the administering of specific compounds that are known to be inhibitors of Mst1 whereas the method of invention of Group II is drawn to *in vitro* or *in vivo* screening of compounds that may after sufficient research be determined to be Mst1 inhibitors and perhaps be useful in treating cardiac disease. The classification of the inventions is accurate and in accordance with USPTO requirements

Therefore the requirement is still deemed proper and is made FINAL. **Claims** 1-33 are pending in this application. **Claims 18-33** are withdrawn from further consideration by the Examiner because these Claims are drawn to non-elected inventions. **Claims 1-17** are currently under examination.

Petition

Petition to remove Shimako Yamamoto from the list of inventors has been acknowledged.

Priority

The current application filed on October 10, 2003 claims priority to provisional application 60/418,002 filed on October 11, 2002.

Specification

The disclosure is objected to because of the following informalities: This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below: Nucleic acid sequences longer than 10 nucleotides and amino acid sequences longer than 4 resides need to be designated with a sequence identifier. Applicants must correct the sequence submissions in the specification on: Page 74, Line 13. It appears that the mentioned sequence is designated in the sequence listing as SEQ ID No: 4, an amendment to the specification including the appropriate sequence identifier with the discussed peptide sequence would overcome the rejection.

Claim Objection(s)

Claims 1-17 objected to because of the following informalities:

In **claims 1-17** Mst1 needs to be spelled out in the first instance of use, for example an accepted version would be, Mammalian Sterile 20-like Kinase 1, "Mst1" and would overcome the rejection.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for A method of treating cardiac disease in a mammal comprising administering to said mammal an effective amount of a compound selected from the group consisting of dominant negative Mst 1 (K594) and XIAP wherein said compound inhibits Mst1, does not reasonably provide enablement for a method of treating cardiac disease in a mammal comprising administering to said mammal an effective amount of a compound or agent that blocks or otherwise inhibits Mst1 or Mst1 pathway. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation

needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the relative skill of those in the art, (5) the predictability or unpredictability of the art, (6) the amount or direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary. Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation

would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406). Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

1.Breadth of the claims.

In regards to the method of the invention and the breadth of the claims the broadest interpretation that applies is a method of treating cardiac disease in a mammal comprising administering to said mammal an effective amount of a compound or agent that blocks or otherwise inhibits Mst1 or Mst1 pathway

2. The nature of the invention.

The invention is a method of treating cardiac disease in a mammal comprising administering to said mammal an effective amount of a compound or agent that blocks or otherwise inhibits Mst1 or Mst1 pathway

3. The state of prior art.

The state of the art provides for a variety of Mst1 inhibitors, such as XIAP; however their effectiveness as compounds useful in a method of treating cardiac disease in subject to further investigation.

4. The relative skill in the art.

The relative skill in the art as it relates to the administering of therapeutic polypeptides used for the treatment, inhibition, prevention or amelioration of pancreatic disorder is characterized by that of a M.D. or Ph. D. level individual.

5. The level of predictability in the art.

There exists a level of predictability in the art with regards to the method of the invention specifically in view of certain compounds that have been established to be Mst1 inhibitor such as XIAP; however the level of predictability in the art in view of any potential compound that may inhibit the Mst 1 pathway with regards to the method of the invention is low. The method of the invention is a method of treating cardiac disease and not simply, a method of inhibiting Mst1, therefore because a compound is known or has been postulated to be a Mst 1 inhibitor, it would not be accurate to assume that the same compound could be used necessarily to treat cardiac disease in lieu of further experimentation .

6. The amount of guidance present.

The applicant have provided some guidance in regards to the method of the invention, specifically in view of such compounds as dominant negative Mst1 (K594) and XIAP, for which the applicants have provided supporting assays that indicate their potential valuable use in a method of treating cardiac disease in a mammal. But many of the suggested compounds by the applicants in the specification on Page 27, Section 0083, require further investigation in order to establish them as useful and effective therapeutic agents that can be administered to a mammal in a method of treating cardiac disease, as the applicants themselves have stated on Page 28 of the

specification, Section 0087, "once a compound that binds Mst1 or otherwise modulates the Mst1 pathway is selected, it can be tested for its ability to modulate cardiac myocyte apoptosis or function".

7. The existence of working examples.

The applicants have provided a variety of examples on pages 53-78, with the most relevant appearing on pages 59-62 and 68 wherein the effectiveness of dominant negative Mst1 (K594) and XIAP as inhibitors of Mst1 used in a method of treating cardiac disease is discussed.

8. The quantity of experimentation necessary.

In the case of the method of invention more experimentation would be required to practice the invention since the specification has not shown to a person skill in the art how to use the invention.

Due to the large quantity of experimentation necessary to provide evidence that all compounds that inhibit Mst1 or the Mst1 pathway will treat cardiac disease, the lack of guidance presented in the specification regarding the same, the absence of a working example directed to same, the unpredictable nature of the invention with regards to the large amount of compounds that may inhibit Mst1 or the Mst1 pathway, the state of the prior art not providing any evidence for a method of treating cardiac disease using all the mentioned compounds that may inhibit Mst1 or the Mst1 pathway, and the breath of the claims which fails to provide particular steps involved in the method of the invention, the specification fails to teach the skilled artisan in the art how to make and use the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-6, 8-10 and 13-14 are rejected under 35 U.S.C. 102(a) as being anticipated by Yamamoto et al., 2001.

Yamamoto et al. teach that to determine whether caspase activation is necessary for the progression of myocyte death induced by chelerythrine, cardiac myocytes were transfused with adenoviral vector harboring XIAP (X-linked inhibitor of apoptosis protein), an endogenous inhibitor of caspase-3, -7 and –9 and that the overexpression of XIAP in cardiac myocytes abolished morphological changes, increases in DNA fragmentation, activation of caspase-3 and myocyte death caused by chelerythrine (Page 1837, Column 2, Paragraph 2, Lines 1-14).

Yamamoto et al. also teach that intravenous injection of chelerythrine activates caspases and promotes apoptosis in adult rat harts *in vivo* and chelerythrine has been

used for many *in vivo* studies to selectively inhibit PKC, results have added cardiac myocyte apoptosis as another *in vivo* effect of chelerythrine and suggest that proapoptotic effects of chelerythrine may potentially affect the interpretation of many experiments using chelerythrine (Page 1846, Column 1, Lines, 2-8).

Thus Yamamoto et al. teach all the elements of **claims 1-6, 8-10 and 13-14** and these claims are anticipated under 35 USC 102(a).

Claims 1-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Han et al., US Patent No: 6,225,288.

Han et al. disclose pharmaceutical compositions comprising compounds of formula I useful as inhibitors of caspase-3, which is implicated in modulating apoptosis (Abstract and Column 3, Lines 1-3). Han et al. teach that an embodiment of the invention encompasses a method of treating a caspase-3 mediated disease in a mammalian patient in need of such treatment, comprising administering to said patient a compound of formula I in an amount effective to treat said caspase-3 mediated disease (Column 83, Lines 42-47). Han et al. teach further that in particular the mentioned compounds are useful to treat, prevent or ameliorate in mammals and in especially in humans, diseases including but not limited to: cardiac and cerebral ischemia/reperfusion injury (e.g. stroke) (Column 84, Lines 42-46).

Thus Han et al. teach all the elements of **claims 1-15** and these claims are anticipated under 35 USC 102(b).

Claims 1-3, 7-9 and 13-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Laugwitz et al., US Patent Publication No: 2003/0130216.

Laugwitz et al. teach that accordingly the invention relates to the use of inhibitor of caspase-3 or caspase-activated deoxyribonuclease (CAD) for the prevention or treatment of cardiac disease, especially insufficiency or the left ventricle (Section 0005, Lines 1-4) and in a preferred embodiment of the present invention, the inhibitor is a compound that inhibits expression of the gene coding for CAD or caspase-3, for example a ribozyme or an antisense RNA (Section 0006, lines 1-6 and in a more greatly preferred embodiment of the invention relates to an antisense RNA which is characteristic in that it is complementery to the mRNA transcribed by the gene coding dor CAD or caspase-3, or a protion of and is able to specifically bind to that mRNA and as a result of which the synthesis of CAD or caspase-3 is reduced or inhibited (Page 2, Section 0007, Lines 1-15) . Laugwitz et al. also teach that the invention is administered to humans (Page 2, Column 2, Lines 12-16 and Section 0010, Lines 1-6).

Thus Laugwitz et al. teach all the elements of **claims 1-3, 7-9 and 13-14** and these claims are anticipated under 35 USC 102(e).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Han et al., US Patent No: 6,225,288 in view of Danilewicz et al. US Patent No: 4,975,444.

Han et al. teach a method of treating cardiac disease as mentioned above.

Han et al. do not teach that their method of treatment includes the administering of beta-blockers, diuretics or angiotensin-converting enzyme (ACE) inhibitors.

Danilewicz et al. teach that their invention relates to a series of cycloalkyl-substituted glutaramide derivatives which are antihypertensive agents having utility in the treatment of various cardiovascular disorders, including hypertension and heart failure. Danilewicz teach further that cycloalkyl-substituted glutaramide derivatives which are inhibitors of the zinc dependent neutral endopeptidase E.C.3.4.24.11 and which are thereby able to potentiate the biological effects of atrial natriuretic factor and in particular, are natriuretic, antihypertensive and diuretic agents of value in the treatment of various cardiovascular disorders (Column 1, lines 1-10).

Danilewicz et al. also teach that the compounds of the invention are also inhibitors of the enzyme E.C.3.4.24.11 and, in addition, they are also able to inhibit angiotensin converting enzyme, a further enzyme which is involved in the control of

blood Pressure and that the compounds thus have a dual pharmacological action through inhibiting two key enzymes involved in blood pressure control which makes them particularly useful in the treatment of various forms of hypertension and associated cardiovascular disorders, e.g. congestive heart failure and glaucoma and as mentioned the compounds of the invention are also inhibitors of angiotensin converting enzyme and as such they are useful in treating a further variety of conditions for which ACE inhibitors are known to be useful including limitation of ischemic damage to the myocardium, protection of the kidney against hyper-filtration damage, prevention or reversal of left ventricular hypertrophy (Column 1, Lines 25-31).

Danilewicz et al. teach that for human use, the compounds of the invention can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice (Column 9, Lines 55-60) and that the compounds may be co-administered with other agents as may be beneficial for the control of blood pressure or the treatment of cardiac conditions or renal insufficiency, thus for example they may be co-administered with digitalis or another cardiac-stimulant drug or with an alpha-blocker, beta-blocker exogenous ANF or with a potassium channel activator or another diuretic agent as shall be determined by the physician as appropriate to the particular patient or disease state (Column 10, Lines 3-11).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine Han et al. and Danilewicz et al. because, "It is prima facie obvious to combine two compositions each of which is taught by the prior art to

be useful for the same purpose, in order to form a third composition to be used for the very same purpose....[T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted).

Claims 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Han et al., US Patent No: 6,225,288 in view of Kukreja US Patent Pub. No: 2004/0009957.

Kurkreja teaches that the invention provides a method to prevent or decrease apoptosis or necrosis caused by ischemic/reperfusion event in cells, tissues or organs. The method includes the step of comprising the step of exposing the cells, tissues or organs to a sufficient amount of a phosphodiesterase-5 (PDE-5) inhibitor to prèvent or decrease apoptosis or necrosis of the cells, tissues or organs. The method may be performed prior to, after, or during the ischemic/reperfusion event. The cells, tissues or organs may located within a patient, and the step of exposing may be performed prior to, during, or after a surgical or interventional procedure. Administration of the PDE-5 inhibitor may be, for example, via intraperitoneal, oral, intravenous, or intracoronary administration to the patient. Further, the method may be used in conjunction with the administration of other drugs. The patient may be a human or a non-human mammal (Section 0013, Lines 1-13).

Kurkreja also teaches that Doxorubicin (DOX) is a powerful anthracycline antibiotic used to treat many human neoplasms, including acute leukemias, lymphomas, stomach, breast and ovarian cancers, Kaposi's Sarcoma, and bone tumors, Doxorubicin may also cause dose-dependent cardiotoxicity often leading to irreversible cardiomyopathy and ultimately congestive heart failure and although recent evidence shows that less toxic doses of Doxorubicin can be used effectively, heart failure in Doxorubicin-treated patients can go undetected for up to 20 years after treatment cessation, causing some cancer patients to be unwilling to use Doxorubicin; therefor this is obviously a serious drawback in the treatment of cancer and however, the invention provides a solution to this dilemma in that the prophylactic administration of PDE-5 inhibitors to a patient undergoing treatment with DOX prevents or lessens the occurrence of Doxorubicin -induced cardiotoxicity (Section 0047, Lines, 1-19).

Kurkreja does not teach that the anti-apoptotic agent used in the method of treatment mentioned above is an inhibitor of Mst1.

Han et al. teaches inhibitors of caspase-3 and Mst1 that are used in a method of cardioprotection (mentioned above).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to co-adminiter an inhibitor of Mst1 with doxorubicin for the advantages lessening the occurrence of Doxorubicin-induced cardiotoxicity as taught by Han et al. and Kukreja, see Kureja at Section 0047, Lines, 15-19.

Prior Art of Record

Robertson et al. United States Patent No: 6,159,948.

Reszka et al. United States Patent No: 6, 416,964.

Allis et al. United States Patent Application Publication No: 2004/0197838.

Matsui et al. States Patent Application Publication No: 2004/0058367.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert B. Mondesi whose telephone number is 571-272-0956. The examiner can normally be reached on 9am-5pm, Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert B Mondesi
Patent Examiner
Group 1653
05-12-05

JON WEBER
SUPERVISORY PATENT EXAMINER